Remarks

Claims 1, 3-6 and 8-11 are pending. No claim has been amended.

Section 112, First Paragraph, Rejections

The Examiner has rejected Claims 1, 3-6 and 8-10 under 35 U.S.C. 112, first paragraph, as lacking written description. This rejection is respectfully traversed.

The Examiner alleges that the claims recite a genus of nucleic acids encoding a *Rhodosporidium cephalosporin* esterase, and that this genus encompasses nucleic acids encoding any cephalosporin, including cephalosporin C, esterase from any species and any strains of Rhodosporidium. The Examiner alleges, therefore, that there is inadequate written description for *Rhodosporidium cephalosporin* esterase. Applicants respectfully point out, however, that the present invention is not claiming *Rhodosporidium cephalosporin* esterase, rather it is directed to a process for the direct production of desacetylcephalosporin C using the stated fungal organism. Accordingly, one of skill in the art would readily be able to determine which *Rhodosporidium cephalosporin* esterases are capable of satisfying the conditions of the claims. Obviously, any such esterase not satisfying the conditions of the present claims would not be within the scope of the present invention.

Accordingly, Applicants respectfully submit that proper written description is provided for the term *Rhodosporidium cephalosporin* esterase and withdrawal of this rejection is proper and respectfully requested.

The Examiner has also rejected Claims 1, 3-6 and 8-10 under 35 U.S.C. 112, first paragraph, as not enabled. The Examiner alleges that the method of use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium cephalosporin C* esterase of SEQ ID NO:2, including SEQ ID Nos: 1 and 3 is enabled, but the specification does not provide enablement for a use of a strain of *Acremonium chrysogenum* transformed with a nucleic acid encoding a *Rhodosporidium cephalosporin C* esterase having an unknown homology to SEQ ID Nos: 1 or 3. This rejection is respectfully traversed.

Applicants again respectfully point out that the present invention is not claiming *Rhodosporidium cephalosporin* esterase, rather it is directed to a process for the direct production of desacetylcephalosporin C using the stated fungal organism. Accordingly, one of skill in the art would readily be able to determine which *Rhodosporidium cephalosporin* esterases are capable of satisfying the conditions of the claims. Obviously, any such esterase not satisfying the conditions of the present claims would not be within the scope of the present invention.

Accordingly, Applicants respectfully submit that one of skill in the art would be able to determine which *Rhodosporidium cephalosporin* esterases work in the present invention. Accordingly, withdrawal of this rejection is proper and respectfully requested.

Section 102 Rejections

The Examiner has maintained the rejection of claims 1, 3-6 and 9-11 under 35 U.S.C. §102(b) as being anticipated by WO 98/12345 ("Politino (A)"). The Examiner continues to allege that Politino (A) teaches a method for producing desacetylcephalosporin C using a cephalosporin esterase from *Rhodosporidium toruloides* (Example 2). This rejection is respectfully traversed.

Applicants again point out that the present invention is for a process for the direct *in vivo* production of desacetylcephalosporin C comprising culturing a strain of *Acremonium chrysogenum* containing both a nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase. The Examiner has not provided a reference which discloses such an a process.

The Examiner continues to rely on Politino (A), which describes the cloning and sequencing of R. toruloides cephalosporin esterase genomic and cDNA genes. However, it does not disclose *Acremonium chrysogenum* containing both a nucleic acid encoding enzymes for cephalosporin C biosynthesis and a recombinant nucleic acid encoding *Rhodosporidium cephalosporin* esterase which is capable of directly fermenting desacetylcephalsoporin C wherein there is less than 40% loss of cephalosporin C due to non-enzymatic breakdown.

In the present invention, the use of the recombinant *Acremonium chrysogenum* fungal organism results in conversion of cephalosporin C to desacetylcephalsoporin C without the loss of cephalosporin C due to non-enzymatic breakdown which normally results from fermentation broth. According to Claim 1, in the present invention the breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%. This is simply not shown in Politino (A). The Examiner alleges that Example 2 in Politino (A) states that because no side products were observed with HPLC, this satisfies the requirement that less than 40% of cephalosporin C is lost. However, Applicants respectfully assert that the Examiner's reliance on Example 2 is misplaced and point out that Example 2 does not disclose the claimed process as required for anticipation, namely the use of the claimed recombinant fungal organism for the fermentation of desacetylcephalsoporin C in which the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%.

Applicants again respectfully point out that for a reference to anticipate the claimed invention, each element of the claimed invention must be disclosed in the reference. Politino (A) simply does not disclose each and every element of the claimed invention, and the Examiner has

not pointed out specifically where the claimed process is disclosed. In response to Applicants' request that the Examiner do so, the Examiner states that *A. chrysogenum* naturally contains nucleic acids encoding enzymes for cephalosporin C biosynthesis and concludes, therefore, that an *A. chrysogenum* transformed with DNA encoding cephalosporin esterase will directly produce both cephalosporin C esterase and desacetylcephalosporin C. However, there is no actual disclosure of the claimed process and therefore no basis on which the Examiner can make this conclusion. The Examiner further states that the claimed conditions for culturing A. chrysogenum are standard and that the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40% due to the fact that no byproducts were seen in HPLC in Example 2. However, Applicants again point out that Example 2 of Politino (A) does not disclose a process of the claimed invention, so it is no clear how this is relevant.

Therefore, Applicants again respectfully point out that the Examiner is merely making suppositions and conclusory statements while misapplying Example 2 in Politino (A) and has still not shown specifically where each and every element of the claimed invention is shown.

Moreover, the Examiner's argument is apparently that expressing cephalosporin esterase in *A. Chrysogenum*, which Politino (A) suggests could be done, is sufficient to anticipate the process of the present invention. Applicants previously pointed out that this cannot be the case, as several additional factors are required in the present invention for an enabled fungal organism capable of carrying out the claimed process. Specifically, Politino (A) merely discloses the cloning of the esterase gene which is required for heterologous expression of an active enzyme, but it does not necessarily follow that the enzyme will be readily expressed in an active form. In fact, efforts to express this enzyme in an *E. coli* host did not result in an active protein, as describe at pages 37-38 of the present specification. The Examiner dismisses this argument, saying that it is not relevant because the claimed process does not use a transformed *E. coli*, but Applicants submit that this point is very relevant as it shows the problems which were solved in the process of the present invention (namely, expressing the esterase in a host cell which is described, but not taught in Politino (A)), which further evidences the fact that the suppositions made by the Examiner (namely, that a host cell actually transformed such as in the present invention would be useful in the inventive process) are unfounded.

To summarize, the only instance in which Politino (A) could anticipate the present invention were if it specifically provided an enabling disclosure of the process of the present invention. But Politino (A) fails to disclose any process at all for the fermentation of desacetylcephalosporin C. The only instance of desacetylcephalosporin C production is found in Example 2, which merely shows the activity of the esterase enzyme produced by *Rhodosporidium toruloides* cells (it has nothing to do with a recombinant fungal organism as claimed in the present invention).

Accordingly, Applicants respectfully submit that withdrawal of the rejection under Section 102 is appropriate and is respectfully requested.

The Examiner has also maintained the rejection of claims 1, 3-6 and 9-11 under 35 U.S.C. §102(e) as being anticipated by US Patent 5,869,309 ("Politino (B)"). Politino (B) is the US counterpart to Politino (A) and the Examiner's reliance on Politino (B) to support a rejection under Section 102 is the same as that of Politino (A). Accordingly, for the same reasons discussed above, Applicants respectfully submit that Politino (B) does not anticipate the claimed invention and withdrawal of this rejection is appropriate and is respectfully requested.

Section 103 Rejection

The Examiner has maintained the rejection of Claim 8 under 35 U.S.C. §103(a) as being unpatentable over Politino (A) or (B) in view of U.S. Patent No. 4,533,632 ("Smith"). The Examiner alleges that Smith teaches a process for the preparation of desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides*. The process of fermentation is carried out at 15°-45° C and pH 4-9. The Examiner alleges that it would have been obvious at the time of the present invention to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C.

Applicants respectfully submit that the Examiner has only made conclusory statements without providing the requisite motivation necessary for a proper rejection under Section 103. In the outstanding Office Action, the Examiner states that Smith is cited for its disclosure of conditions for culturing of *Acremonium chrysogenum*. However, in the 103 rejection, the Examiner states that it would have been "obvious to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C." Therefore, Applicants again submit that the Examiner has not shown why this would be obvious nor provided any motivation to support such an allegation. If Smith is merely being cited for its disclosure of conditions for culturing of *Acremonium chrysogenum*, as stated by the Examiner, it is not understood how this provides the motivation "to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C" which is the stated rejection under Section 103.

In any event, the present invention is directed to a process for the direct production of desacetylcephalosporin C by using the claimed fungal organism to achieve the claimed results. As discussed previously, neither Politino (A) nor (B) teach or disclose such a process. Smith, therefore, cannot remedy the deficiencies of either of these references.

Accordingly, Applicants respectfully submit that withdrawal of the rejection under Section 103 is appropriate and is respectfully requested.

Conclusion

In view of the amendments and remarks above, Applicants submit that the claims are in condition for allowance and favorable action is therefore respectfully requested.

Please direct any questions regarding this reply to the undersigned attorney.

Respectfully submitted,

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Date: December 22, 2004